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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
KIM, YOUNG J	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 07/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/080,795	KAMME ET AL.	
	Examiner	Art Unit	
	Young J. Kim	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 May 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-14 and 16-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-14 and 16-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/26/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The present Office Action is responsive to the Amendment received on May 2, 2006.

Preliminary Remark

Claims 3, 15, and 24-26 are canceled.

Claims 1, 2, 4-14, and 16-23 are pending and are under prosecution herein.

Information Disclosure Statement

The Office acknowledges the IDS received on February 16, 2006.

A signed copy of the PTO-1449 is enclosed herewith.

Claim Rejections - 35 USC § 103 - Maintained

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection of claims 1, 2, 4-14, and 16-23 under 35 U.S.C. 103(a) as being unpatentable over Mack et al. (U.S. Patent No. 6,566,502 B1, issued May 20, 2003, filed June 30, 2000) in view of Legerski (U.S. Patent No. 6,406,891 B1, issued June 18, 2002, filed September 28, 1998), made in the Office Action mailed on December 27, 2005 is maintained for the reasons of record.

Applicants' arguments presented in the Amendment received on May 2, 2006 have been fully considered but they are not found persuasive for the reasons set forth in the, "Response to Arguments" section.

The Rejection:

Mack et al. disclose a method of producing cRNA from samples, said method comprising the steps of:

(a) synthesizing a first strand cDNA from total RNA or polyA+ mRNA by contacting said RNA or polyA+ mRNA with T7-T24 oligo (or a first primer) and SuperScript™ RT (or reverse transcriptase) (column 44, lines 33-41);

(b) synthesizing a second strand cDNA via contacting the synthesized first cDNA strand with *E. coli* DNA polymerase and RNase H (column 44, lines 42-54); and

(c) In vitro Transcription (IVT) of cDNA into cRNA by contacting the synthesized double stranded cDNA with a T7 RNA polymerase (column 45, lines 1-16).

Mack et al., in producing a second cDNA strand, do not explicitly use Bst DNA polymerase, large fragment, and incubation conditions thereof (claims 2, 4, 6, 12, and 17).

Legerski discloses a method of synthesizing double stranded cDNA from RNA, wherein the method involves the steps of:

a) reverse transcribing mRNA from a sample via use of a reverse transcriptase (column 2, lines 40-46), resulting in a first strand cDNA; and

b) synthesizing a second strand cDNA via use of dNTPs and DNA polymerase (column 2, lines 46-52), thereby forming double stranded cDNAs.

Legerski, in discussing the invention explicitly states that by "exploiting a combination of (a) processive enzymes at a lower temperature to increase the length of the first strand of the cDNA and (b) thermostable enzymes at a higher temperature to remove the secondary structure formed in the first strand [cDNA], the present invention provides an effective method of producing long cDNA moieties in an reverse transcription-based synthesis method." (column 6, lines 50-56),

wherein one of the polymerases contemplated for the method is (column 11, lines 49-53), is Bst DNA Polymerase, Large Fragment (column 11, lines 54-55).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made combine the teachings of Mack et al. with the teachings of Legerski, thereby arriving at the claimed invention for the following reasons.

All of the steps claimed by the instant claim are disclosed by Mack et al., excepting that the polymerase used for second strand cDNA synthesis is an *E. coli* DNA polymerase. Specifically, Mack et al, in generating the 2nd strand of the cDNA, employ *E. coli* DNA polymerase. Consequently, Mack et al. would not disclose a condition that is suitable for a second strand cDNA synthesis involving Bst DNA polymerase large fragment.

However, Legerski specifically improves the method of generating double stranded cDNAs, wherein the artisan specifically recognizes the problem associated with generating a second strand cDNA synthesis from a first strand cDNA, that is, the formation of secondary structure. Legerski specifically overcomes this problem by use of a thermostable DNA polymerase in the second strand cDNA synthesis step, specifically contemplating Bst DNA polymerase large fragment, allowing for the synthesis of long cDNA molecules (column 6, lines 50-57).

Hence, one of ordinary skill in the art would have been motivated to employ the teachings of Legerski in the method of generating the double stranded cDNA molecules of Mack et al., for the above discussed benefit in generating second strand cDNA molecules from its first strand cDNA, the RT part of the RT-PCR method provided by Mack et al. with a reasonable expectation of success.

With regard to claims 2 and 17, given the fact that Legerski discloses the use of Bst DNA polymeras large fragment for second strand cDNA synthesis, one of ordinary skill in the art would

have been able to determine the optimal temperature at which to conduct this step. In addition, however, Legerski explicitly discloses that Bst DNA polymerase should not exceed 70°C (column 12, lines 9-10).

With regard claims 4, 6 and 12, the concentrations of the Bst DNA polymerase large fragment and RNAse, given the fact that Bst DNA polymerase is employed, the optimal concentration or incubation temperature under which the method is conducted is obvious under the routine optimization, as provided for by MPEP 2144.05(II).

> "A. Optimization Within Prior Art Conditions or Through Routine Experimentation Generally, *differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art* ***unless*** there is evidence indicating such concentration or temperature is ***critical***. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (Claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% was held to be prima facie obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%.); >see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known ***provides the motivation to determine*** where in a disclosed set of percentage ranges is the optimum combination of percentages.");< ** In re Hoeschele, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969) (Claimed elastomeric polyurethanes which fell within the broad scope of the references were held to be unpatentable thereover because, among other reasons, there was no evidence of the criticality of the claimed ranges of molecular weight or molar proportions.). For more recent cases applying this principle, see Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); In re Kulling, 897 F.2d 1147, 14 USPQ2d 1056 (Fed. Cir. 1990); and In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997)."

Hence, it would have been well-within the purview of an ordinarily skilled artisan at the time the invention was made to be motivated to determine the optimum incubation condition, *i.e.*, temperature and the incubation time, as well as the enzyme concentration, through routine

optimization, provided that Legerski disclose the use of Bst DNA polymerase large fragment in generating second strand cDNA molecules, thereby arriving at the claimed invention.

With regard claim 5, Mack et al. employs labeled Bio-11-UTP and Bio-16-CTP (column 45, lines 11-13).

With regard claims 7, 8, 9, 10, and 18, Mack et al. states that the nucleic acids could be labeled with Cy_3 or Cy_5 (column 17, lines 16-20; column 31, lines 40-43).

With regard to claims 11, 22 and 23, the labeled cRNA are hybridized on an array of nucleic acid probes to determine the differential expression of CZA8 (column 48) in tumorous (thus pathologically aberrant) and normal samples (thus pathologically non-aberrant; *see* column 59, claim 1).

With regard to claims 13 and 19-21, while Mack et al. are not explicit in disclosing how many polynucleotides probes are immobilized on their array, Mack et al. disclose that known commercial arrays could be used in their method, including Affymetrix GeneChip™ (column 26, line 26), which is known in the art to comprise over 1,000 probes/cm^2. According to *In re Best* 195 USPQ 430, 1997, the court stated that, "Patent Office can require applicant to prove that prior art products do not necessarily or inherently posses characteristics of his claimed product wherein claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes; burden of proof is on applicant" (pp. 430). Absent evidence to the contrary, the density of the array claimed by the instant application is determined to be met by Mack et al.

With regard to claim 16, the samples employed are from human patient (thus mammalian; *see* column 4, lines 23-30).

Therefore, for the above reasons, the invention as claimed is *prima facie* obvious over the cited references.

Response to Arguments:

Applicants contend that Legerski's teachings are drawn to the reduction of secondary structure in an mRNA during the first strand cDNA synthesis and not during the second cDNA strand synthesis (page 8, 3rd paragraph, Response). Applicants based on this contention, state that the teachings of Legerski is focused on improving the process of making full-length cDNA from long mRNA by temperature cycling in first strand synthesis to remove mRNA secondary structure during that step, and that although ***Legerski teaches that Bst DNA polymerase large fragment can be used in second strand synthesis***, Bst1 thermostable is offered among a laundry list of DNA polymerases, some of which are thermostable and some of which are not (page 9, 2nd paragraph, Response).

Applicants thus conclude that the rejection fails to provide any motivation for selectively choosing Bst1 DNA polymerase from the various DNA polymerases disclosed in the prior art, and that Legerski does not even recommend Bst DNA polymerase from thermal cycling in the first strand synthesis, and even goes so far as to note that Bst DNA polymerase cannot be used for thermal cycle sequencing." (page 9, 2nd paragraph, Response).

Applicants' arguments are not found persuasive.

Initially, it should be noted that Applicants do not dispute that Legerski does in fact, disclose the use of Bst1 DNA polymerase in the second strand cDNA synthesis involved in the PCR portion of the RT-PCR reaction (see Applicants' response on page 9, 2nd paragraph, Response).

Initially, if Applicants are contending that a prior art disclosure must provide explicit example of all of the contemplate embodiments for being prior art, Applicants are clearly wrong.

Were Applicants' arguments be valid, a patent document which discloses a PCR reaction, wherein the DNA polymerase is disclosed as being well known polymerases, while disclosing a

single example employing Taq polymerase, would not be prior art against claims which are drawn to one of the contemplated species of DNA polymerases.

Such is not true.

In addition, if Legerski et al. explicitly discloses that the formation of secondary structure in the mRNA is problematic in generating a first strand cDNA, it would be entirely reasonable for one of ordinary skill in the art at the time the invention was made to recognize that the first strand cDNA which is produced from the mRNA, which comprises the complementary sequence of the mRNA which is explicitly known to be problematic in secondary structure formation, would also be problematic as a template for its propensity to form secondary structure in the second strand cDNA synthesis.

Clearly, one of ordinary skill in the art at the time the invention was made would have been motivated based on the teachings provided for by Legerski et al., as well as having a reasonable expectation of success at employing the very species which Legerski et al. discloses as one of the polymerases useful in generating the second strand cDNA.

Lastly, the list of DNA polymerases disclosed by Legerski et al. is as much of a laundry list as the list of DNA polymerases contemplated by the instant application.

Legerski et al. contemplates Bst DNA polymerase large fragment, Bst DNA polymerase, VENT$_R$®, DEEP VENT, T7 DNA polymerase, DNA polymerase I, Klenow fragment, Taq, and Tf1.

The instant application contemplates Taq, native Bst DNA polymerase, Pfu, Tgo, Phi29, T7, Klenow fragment DNA polymerases (section [0049]).

With regard to Applicants statement regarding how Legerski et al. state that Bst DNA polymerase cannot be used for thermal cycle sequencing" (page 9, 2nd paragraph, Response),

Applicants are correct. However, it should be noted that Legerski et al. is stating that when employing Bst DNA polymerase, and not Bst DNA polymerase large fragment.

In addition, even if the artisans were referring to the large fragment of Bst DNA polymerase, the artisans explicitly state that temperature ***above 70° is not recommended*** (column 12, lines 9-10).

Applicants claims require a broad range of 45 to 80° C, which is well within the temperature of the Bst DNA polymerase of Legerski et al.

For the above reasons, the invention as claimed is obvious over the cited references and the rejection is maintained for the reasons of record.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Inquiries

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Young J. Kim whose telephone number is (571) 272-0785. The Examiner is on flex-time schedule and can best be reached from 8:30 a.m. to 4:30 p.m (M-W and F). The Examiner can also be reached via e-mail to Young.Kim@uspto.gov. However, the office cannot guarantee security through the e-mail system nor should official papers be transmitted through this route.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Dr. Gary Benzion, can be reached at (571) 272-0782.

Papers related to this application may be submitted to Art Unit 1637 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant does submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office. All official documents must be sent to the Official Tech Center Fax number: (571) 273-8300. For Unofficial documents, faxes can be sent directly to the Examiner at (571) 273-0785. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Young J. Kim
Primary Examiner
Art Unit 1637
7/24/2006

YOUNG J. KIM
PRIMARY EXAMINER

YJK